This report is based on a workshop, “Antibiotic Resistance: Current Status and Future Directions,” held at the American Society for Microbiology headquarters in Washington, D.C., July 6, 1994. At the workshop, members of the ASM Task Force on Antibiotic Resistance, which includes scientists from academe, government and industry, considered questions related to research and training, prevalence and major factors affecting the emergence of antibiotic resistance, and surveillance strategies for monitoring resistance in community and hospital settings at national and global levels.
The American Society for Microbiology (ASM), the oldest life science society in the world, represents over 40,000 members. ASM members include scientists in medical microbiology (infectious and immunological diseases), molecular biology and genetics, industrial and food microbiology, biotechnology and public health, agriculture, water purification and waste treatment, environmental science, dental microbiology, veterinary medicine, and education and regulatory activities.

The membership of ASM is gravely concerned about the national and global increase in antibiotic resistance and the complex issues surrounding this public health threat. Infections caused by resistant pathogens result in morbidity and mortality from treatment failures and increased health care costs as newer, more expensive antibiotics are needed to treat common infections. As resistance spreads, involving more antibiotics and more pathogens, infections may occur which cannot be treated effectively with antibiotics. Due to increasing drug resistance in animal pathogens and changes in food production practices, there is a growing threat to food, the food industry, and hence the U.S. economy. Due to increased foreign trade, travel, and immigration, the threat of global spread of antibiotic resistance is greater than ever.

Because of these concerns, the Public and Scientific Affairs Board of ASM convened a task force composed of expert scientists (see Appendix A) from the academic, government, and industrial sectors. The task force considered the current prevalence of antibiotic resistance, major factors affecting the emergence of antibiotic resistance, future research needs and future surveillance strategies for monitoring resistance. The conclusions and recommendations of this group are presented below.

Findings and Conclusions

Although defining the precise public health risk of emergent antibiotic resistance is not a simple undertaking, there is little doubt the problem is global and very serious. Some of the more striking examples include the following.

Today, in the U.S., more than 90% of strains of Staphylococcus aureus (one of the most common disease-producing organisms in humans) are resistant to penicillin and other beta-lactam antibiotics (1).

According to the National Centers for Disease Control and Prevention (CDC) the incidence of vancomycin-resistant enterococci in the U.S. increased 20 times from January 1989 to March 1993 (2). Enterococci are the most common cause of hospital-acquired infections, and vancomycin is often the last weapon available against these potentially deadly microbes.

Before 1987, antibiotic-resistant Streptococcus pneumoniae (“pneumococci”) were uncommon in the U.S. Recent reports document an alarming increase in pneumococcal infections resistant to commonly used antibiotics (3). Pneumococci are the leading cause of pneumonia, meningitis, and bloodstream infections in the elderly and the leading cause of middle ear infections in children. These infections are treated empirically, during the critical initial days of therapy. In order to choose the optimal antimicrobial drug for initial therapy, physicians need to know the pattern of drug resistance of pneumococci circulating in their community.
Medical care costs associated with treating infections in humans due to antibiotic-resistant microorganisms are estimated to be over $4 billion annually in the U.S. (CDC, unpublished data).

- While appropriate antimicrobial drug use has unquestionable benefit, often these agents are used inappropriately by physicians and the public. Inappropriate use results from physicians providing antimicrobial drugs to treat viral infections, using inadequate criteria for diagnosis of infections that potentially have a bacterial etiology, unnecessarily prescribing expensive, broad-spectrum agents, and not following established recommendations for using chemotherapy. It is also likely that patients or, in the case of children, their parents contribute to antimicrobial misuse by pressuring physicians to provide treatment.

- Fueling the excessive use of broad-spectrum antimicrobial drugs is an absence of reliable diagnostic tests that enable physicians to accurately discern when antimicrobial drugs are not needed. When antimicrobial drug therapy is needed, improved diagnostic tests would lead to use of more targeted antimicrobial drugs, resulting in a reduction in the widespread administration of broad-spectrum drugs.

- Selective pressure exerted by widespread antimicrobial use is the driving force in the development of antibiotic resistance. The association between increased rates of antimicrobial use and resistance has been documented for nosocomial infections in hospital-based studies (4) and for resistant community-acquired infections in studies associating rates of drug use on a regional or national basis with resistance patterns (5). In addition, case-control studies have shown antimicrobial use as a significant risk factor for infection with a resistant pathogen (6, 7).

- According to the CDC, most antimicrobial use in humans is for treatment of outpatient infections. In 1992, an estimated 110 million courses of antimicrobial therapy were prescribed by office-based physicians in the U.S., a 28% increase over the number in 1980 (8).

- While antimicrobial drugs are provided to persons of all ages to treat a variety of conditions, the best data are available for the pediatric population. Data from the National Center for Health Statistics indicate that the rate of antimicrobial use in children (below age 15) is more than 3 times greater than the rate for any other age group “within the population (8). In addition, the leading diagnoses resulting in antimicrobial prescriptions in 1990 were all common pediatric infections, including otitis media, upper respiratory infection, bronchitis, sinusitis, and pharyngitis.

- Otitis media is the second leading cause of office visits to physicians (24.5 million visits in 1990) (9) and the leading cause of emergency room visits (10). This diagnosis accounts for over 40% of all outpatient antimicrobial use in children (11).

- As the leading bacterial causes of otitis have developed resistance to “first-line” antibiotics, therapy with new, broader-spectrum, more expensive antibiotics has increased. The significance of the resulting selective pressure extends far beyond its potential impact on resistance in otitis media. Resistance among pathogens such as S. pneumonia affects persons of all ages who have pneumococcal infections, including pneumonia, bacteremia, and meningitis. Antimicrobial use for otitis media and other upper respiratory infections also exerts selective pressure on other bacterial species that colonize the respiratory and gastrointestinal tracts which are not etiologic agents of otitis media, such as Staphylococcus, Gram-negative enteric organisms, and enterococci.

- In 1988, the National Academy of Sciences/Institute of Medicine estimated that nearly half of the total annual production of antibiotics is directed to use in farm animals (12).

- Due to changes in management practices (i.e., consolidation of animal production in very large facilities instead of small-scale family farms), there is also a growing concern related to
animal health, antibiotic resistance, and therefore food production in this country. Conditions are such that diseases can spread rapidly through a large number of animals in a herd or flock, sometimes with dire economic consequences. As is the case for diseases in humans, the number of therapeutic options for treatment of diseases in animals (both farm and domestic) is diminishing.

Increasing reliance on aquiculture for food production, the increasing problems associated with infectious diseases in fish, the limited number of drugs available for treatment and prevention of these diseases, and the rapid increase in resistance to these antibiotics represent major challenges for this source of food production worldwide.

Resistance factors in human and animal pathogens, particularly those carried on mobile elements, can spread rapidly within human and animal populations and from animals to humans, particularly in contaminated food products.

Resistance to antimicrobial drugs is a global problem. Multidrug-resistant pathogens not only travel locally but also traverse the globe. Due to increased international travel and increased foreign trade of fresh food products, the threat of global spread of antibiotic resistance is greater than ever before.

The relative utility of available antibiotics is eroding, tipping the balance in favor of multidrug-resistant pathogens, and there appear to be few new drugs in the pipelines of U.S. pharmaceutical companies. These developments amount to an incipient public health emergency, albeit one that is poorly appreciated or recognized.

Currently there is no national or global surveillance system for monitoring antibiotic resistance in animals or humans. In fact, the amount being expended is totally inadequate. The last survey, which was conducted in 1992, indicates that a total of less than $55,000 is spent in the U.S. for antibiotic resistance monitoring in human pathogens at the federal, state, and local levels (13). The task force concluded that due to the lack of a national surveillance system, current data related to the incidence of antibiotic resistance represent only the tip of the iceberg. There are even fewer data available on the incidence of antibiotic resistance in animal pathogens. Therefore, the magnitude of the problem has likely been underestimated.

Emphasis in developed countries should be placed on the availability of safe and effective antibiotics and the enforcement of more responsible national drug policies. Success will require the collective action of governments, the pharmaceutical industry, health care providers, and consumers.
SUMMARY OF RECOMMENDATIONS

A national surveillance system should be established immediately.

- Federal funding should be immediately allocated for the establishment of a national system for the surveillance of antibiotic resistance in animals, humans, and food products. The lead agency should be the National Center for Infectious Diseases of the CDC. Other agencies, specifically the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH), the U.S. Department of Agriculture, the Environmental Protection Agency, and the Food and Drug Administration, should be involved in establishing priorities and implementation of regulatory policies related to antibiotic resistance. These agencies should receive additional funding for this purpose. None of these federal agencies have adequate funding to address the magnitude of current problems related to antibiotic resistance.

Professional and public education should be strengthened in the area of infectious diseases and antibiotics to reduce inappropriate usage of antibiotics.

- An urgent need exists for more appropriate selection and use of antimicrobial drugs. The curriculum of health professional (medical, dental, nursing, and veterinary) schools and postgraduate educational programs should be strengthened in the areas of sterilization, disinfection, hazards of inappropriate antimicrobial drug use, appropriate diagnosis and treatment of infectious diseases, and antibiotic resistance. These efforts should result in reduction of spread of infectious agents and more prudent use of antibiotics.

- Better guidelines should be established and enforced to reduce the spread of infectious agents and antibiotic resistance in the hospital environment, nursing homes, day care facilities, and food production industries.

- Educational materials should be developed and widely distributed to patients and food producers. The need for partnerships in re-proving antimicrobial use for cost-effective treatment of infections and to preserve the effectiveness of antimicrobial drugs for the future should be emphasized.

There is an urgent need for more basic research directed toward development of new antimicrobial compounds, effective vaccines, and other prevention measures.

- In FY 1994 allocations to the National Institute of Allergy and Infectious Diseases of the NIH for funding of non-AIDS infectious disease research were reduced by $20 million. Increased appropriations are urgently needed to fund areas of research directly related to new and re-emerging infections and antibiotic resistance.

- More basic research is needed to delineate the genetic and metabolic pathways, including essential regulatory factors, that determine virulence as well as antibiotic susceptibility or resistance in pathogens of human and veterinary importance. To conduct this research, better, more consistent measures of antibiotic resistance are needed, and a culture collection containing representative antibiotic-resistant biotypes and genotypes should be developed and made available for researchers worldwide. Such studies are expected to help in identifying novel targets for molecules that interfere specifically with essential physiological steps of pathogenesis.
● More resources should be devoted to the sequencing of the entire genome of microbial pathogens in an attempt to identify common antimicrobial targets.

● More basic research is needed to determine the mechanisms of spread of pathogens, particularly in closed populations (i.e., hospitals, child care facilities, and food production facilities).

● More basic research is needed to better understand the genetics of microorganisms and the development of antibiotic resistance, particularly in fungi and newly described pathogens.

● Research is needed for development of rapid, reliable diagnostic techniques for identifying specific infectious causes of illnesses. More clinical and epidemiologic research is needed to determine the clinical impact of infection with drug-resistant pathogens and to identify the optimal therapeutic options for treatment of infection with a drug-resistant strain. More clinical research is needed to clarify the etiology of otitis and respiratory infections in all age groups.

● The laws of evolution dictate that microbes will eventually develop resistance to nearly every antibiotic. Thus, more basic research is needed to facilitate development of effective vaccines and other prevention measures. Vaccines are the most cost-effective method of disease control and prevention for many diseases.
Definition of the Problem of Antibiotic Resistance

Although defining the precise public health risk of emergent antibiotic resistance is not a simple undertaking, there is little doubt that the problem is global and very serious.

Antibiotic resistance results in morbidity and mortality from treatment failures and increased health care costs. Current costs related to treatment of infections with antibiotic-resistant organisms are estimated by the National Centers for Disease Control and Prevention (CDC) to be over $4 billion annually. As resistance spreads, involving more and more infectious agents, the concern is that infections may occur which cannot be effectively treated with antimicrobial drugs. Also, of growing concern is the impact of antimicrobial resistance upon the food production industry and food safety in the U.S.

When penicillin was introduced in 1940, virtually all strains of *Staphylococcus aureus*—bacteria associated with pneumonia, bronchitis, abscesses, and osteomyelitis—were susceptible to this antibiotic. Today, more than 90% of strains of this organism are resistant to penicillin and other beta-lactam antibiotics (1). In addition, *enterococci*—the second leading cause of hospital-acquired infections—have developed resistance to *vancomycin*. The incidence of *vancomycin*-resistant *enterococci* associated with hospital-acquired infections increased 20 times from January 1989 to March 1993, according to the CDC. Increasing resistance to *vancomycin* is alarming, since this antibiotic is often the last weapon the physician has against this potentially deadly microbe (2). A great fear is that these microorganisms will transfer the resistance factor for *vancomycin*, which represents the last effective antibiotic for many common infectious diseases, to other, more frankly virulent bacterial pathogens such as *S. aureus*. Due to resistance to penicillin, *aminoglycosides*, and other agents, infections with *vancomycin*-resistant strains are essentially untreatable (2). There are other parts of the world where treatment of some forms of bacterial intestinal infections and gonorrhea is now limited to a single effective antibiotic.

Medical experts duly noted the appearance of antibiotic-resistant *Streptococcus pneumoniae* in New Guinea as early as 1967 but concluded that the microorganisms were not likely to spread and thus posed little threat to the general population. This prediction was erroneous. Drug-resistant *pneumococcal* infections became prevalent in South Africa in the 1970s and in Europe in the 1980s. These strains are becoming increasingly prevalent in the U.S. in the 1990s (3). This is of major concern because *S. pneumoniae* infections are among the leading causes of illness and death among young children, persons with debilitating medical conditions, and the elderly worldwide.

Although the infections caused by antibiotic-resistant pathogens cause serious problems in the general population, such infections can be particularly devastating for the very young, the elderly, and the immunocompromised. With respect to these patient populations, antimicrobial resistance is becoming a major concern in treating fungal infections. Currently, 10% of all nosocomial bloodstream infections are caused by *Candida* species, with an attributable mortality of 38%. The overall rate of candidemia is 5 to 10 per 10,000 hospital admissions; the rate is much higher in high-risk patients (14). High-risk patients include those who are immunosuppressed, such as those with leukemia, solid tumors, and neutropenia, bone marrow transplant patients, premature infants, and burn patients.

It was recently reported that 23% of 157 orthotopic liver transplant patients experienced disseminated fungal infections and that these infections contributed to the deaths of 13% of the 157 (58% of those infected) (15). The excess length of hospital stay due to *Candida* infections can be greater than 30 days at an average cost of $1,200 per hospital day per patient. Resistance to *fluconazole* has been increasing for *Candida albicans* from mucocutaneous disease in HIV-positive patients in France for the past four years. There appears to be both clinical and microbiological resistance.

Antibiotic resistance is a threat not only to human health from the standpoint of treatment of infectious diseases but also to our economic health because of the emerging threat to food production. During the past two decades, U.S. production of poultry, beef, and swine has consolidated under corporate direction, with animals typically concentrated in very large facilities instead of on small-scale family farms. For instance, a typical farm with a corporate affiliation may house 100,000 chickens. In such settings, strong management techniques are emphasized as a way of minimizing and controlling infectious diseases. However, conditions are such that diseases can spread rapidly through a large number of animals in a herd or flock.
sometimes with dire economic consequences. As is the case for diseases in humans, the number of thera-
pic options for treatment of diseases in animals (both farm and domestic) is diminishing. The increasing
reliance on aquiculture for food production in this country, the increasing problems associated with infec-
tious agents, and the limited number of drugs available for treatment and prevention of infectious diseases
in fish represent some of the most difficult challenges in antibiotic resistance and food production.

Antibiotic-resistant pathogens in animals not only pose a concern with respect to animal health but also
pose a growing concern regarding possible transmission to humans as food-borne pathogens. The role of
animals as primary sources of human disease has now been documented (e.g., campylobacters in contami-
nated poultry, Salmonella serotype enteritidis in eggs, and vibrios in fish) (16, 17). Food-borne illness asso-
ciated with fruits and vegetables is also increasing in this country.

Ironically, as the incidence of disease related to bacterial pathogens and antibiotic resistance is increasing,
the search for new drugs or other novel agents to combat bacterial pathogens has lost much of its momen-
tum in recent years. Advances in chemistry and biochemistry as well as the availability of rapid screening
methods mean that tens of thousands of chemical derivatives can now be looked at rather quickly and at
least superficially evaluated in large numbers. Significant effort has been expended toward understanding
mechanisms of resistance in order to identify new targets based on fundamental cellular/virulence proper-
ties and thus to design screens which specifically address those targets. Despite the availability of such new
screening methods, this approach has not uncovered a new and widely useful family of antibiotic drugs
since the fluoroquinolones came into clinical use a number of years ago.

Given these forces, the relative utility of available antibiotics is eroding, tipping the balance in favor of
multidrug-resistant pathogens. These developments amount to an incipient public health emergency, albeit
one that is poorly appreciated or recognized. Early successes during the antibiotic era helped to foster
widely held beliefs among researchers, the medical community, and the general population that infectious
diseases would soon be conquered and that research and public health attention could safely shift to other
problems. Reversing that general perception and overcoming the complacency that has grown up around it
are not easy undertakings but ones which must be accomplished.

Emergence and Spread of Antibiotic Resistance

The laws of evolution dictate that microbes will eventually develop resistance to practically any antibiotic. Selec-
tive pressure exerted by widespread antimicrobial use is a driving force in the development of antibiotic resis-
tance. The association between increased rates of antimicrobial use and resistance has now been documented
for nosocomial infections in hospital-based studies (4) and for resistant community-acquired infections in studies
associating rates of drug use on a local or national basis with resistance patterns (5). In addition, case-control
studies have shown antimicrobial use as a significant risk factor for infection with a resistant pathogen (6, 7).

According to the CDC, most antimicrobial use in humans is for treatment of outpatient infections. In
1992, an estimated 110 million courses of antimicrobial therapy were prescribed by office-based physicians
in the U.S., a 2870 increase over the number in 1980 (8).

Factors contributing to the emergence of antibiotic resistance differ depending upon geographic location.
Over-the-counter use of antibiotics and their use as “folk” remedies have contributed to antibiotic resis-
tance in developing countries. In other areas, antibiotic abuse in prophylactic and empiric therapy and mis-
use of the newest drugs for questionable indications in the community have been major contributors.

Due to a number of factors, including the critical state of the patient, physicians are often forced to use
antibiotics empirically, prior to receiving test results which routinely take several days to process. Predict-
ing the cause of disease without laboratory test results is risky because one or more organisms may be in-
volved. Such use of antibiotics contributes to development of resistance. There is concern that new cost
containment pressures may also impede appropriate management of infections if physicians must select
antibiotics that are on a hospital’s formulary. Widespread use of oral antibiotics for treatment of acne and
other mild conditions is of growing concern.

Inappropriate use of antibiotics results from application of inadequate criteria for diagnosis of infections
that potentially have a bacterial etiology, unnecessarily prescribing expensive, broad-spectrum agents, and
not following established recommendations for using chemoprophylaxis. It is also likely that patients or, in
the case of children, their parents contribute to antimicrobial misuse by pressuring physicians to provide
treatment. The reduced time in the medical school curriculum devoted to basic microbiology and principles of infectious diseases has undoubtedly contributed to these problems.

While antimicrobial drugs are provided to persons of all ages to treat a variety of conditions, the best data are available for the pediatric population. Data from the National Center for Health Statistics indicates that the rate of antimicrobial use in children below age 15 is more than 3 times greater than in any other age group within the population (8). In addition, the leading diagnoses resulting in antimicrobial prescriptions in 1990 were all common pediatric respiratory infections, including otitis media, upper respiratory infection, bronchitis, sinusitis, and pharyngitis.

Otitis media (ear infection) is the second leading cause of office visits to physicians (24.5 million visits in 1990) (9) and the leading cause of emergency room visits (10). This diagnosis accounts for over 40% of all outpatient antimicrobial use in children (11). As resistance to first-line antibiotics has developed in the leading bacterial pathogens that cause otitis media, therapy with new, more expensive, broader-spectrum cephalosporins and combination agents has increased. Pharmacy records of two health maintenance organization (HMO) practice plans indicate that in 1993 and 1994, 24 and 17%, respectively, of children with otitis media had been treated with cephalosporins and combination agents. The significance of the resulting selective pressure extends far beyond its potential impact on resistance in otitis media. Resistance among pathogens such as S. pneumoniae affects both children and adults with other pneumococcal infections, including pneumonia, bacteremia, and meningitis. Selective pressure also would be exerted on other colonizing bacterial species that are not agents of otitis media, such as Gram-negative enteric organisms and enterococci.

Resistance factors, particularly those carried on mobile elements, can spread rapidly within human and animal populations and to a certain extent the environment. Multidrug-resistant pathogens travel not only locally but also globally. For example, a specific strain of S. pneumoniae, resistant to multiple antimicrobial drugs, was observed first in South Africa in 1977. Since then, as evidenced by its molecular signature, it has become the commonly identified multidrug-resistant form of S. pneumoniae in a variety of distant settings, including Spain, the United Kingdom, and Iceland (3).

In various regions of the world, one area may become overrun with multidrug-resistant pathogens, whereas a neighboring area may be relatively unaffected or, at least temporarily, spared. On the Iberian Peninsula, for instance, Portugal is relatively free of penicillin-resistant forms of pneumococci, whereas such pathogens are common in neighboring Spain. Similarly, within Hungary, the overall prevalence of these penicillin-resistant S. pneumoniae is moderate to high at 35 to 40%, but that average varies considerably from county to county, with far higher rates in regions bordering Ukraine, where poverty is common. Within the U.S. the prevalence of antibiotic resistance can vary tremendously even within hospitals within the same city. Increased travel, both foreign and domestic, fosters spread of organisms, disease, and antibiotic resistance (18). Over 100 million people currently live outside the countries in which they were born (19).

Commercial movement of fruits and vegetables from one country to another also redistributes microorganisms and their resistance factors. There is a rapid increase in food-borne diseases in this country. In 1992, there were over 9,000 deaths attributable to food-borne bacteria (CDC, unpublished data).

Many unanswered questions surround the role of animals and the microbiota and the contribution to the problem of antibiotic resistance. However, the need for increased production of fish and the increasing use of aquaculture represent one of the biggest concerns. First, this commercial activity is growing in volume but practices are far from standardized or regulated. Second, when antibiotics are used in aquiculture settings, the drugs typically remain in the open environment and may flow out of growth ponds into open waterways or sewage systems to become widely disseminated environmental contaminants. Third, the antibiotics used are the same as those used to treat human infection. Antibiotics specific for fish have not been considered economical to produce. The impact of all these factors on the overall emergence of antibiotic resistance is unknown. However, recent studies indicate that the level of resistant bacteria in the gut of wild fish in nearby ponds is affected during antimicrobial treatment of farmed fish. Furthermore, these studies convincingly demonstrate an increase in resistant bacteria in the intestines of fish receiving antimicrobial drugs. A total of 74 to 100% of wild fish in close proximity to treated ponds contained quinolone residues (20). Furthermore, prior to medication 0.6 to 1.0% of the fecal bacteria in wild fish were resistant to oxacillin and oxytetracycline, respectively. After termination of medication with oxacillin, 46% of the fecal bacteria were resistant to oxacillin and 2096 were resistant to oxytetracycline.

Current Surveillance and Status of U.S. Public Health Infrastructure

At the national level, the CDC in collaboration with local, state, and territorial public health departments currently track a number of reportable infectious diseases in humans. However, even when infectious dis-
eases are reported, drug resistance patterns of the pathogenic organisms involved may not be, meaning that special studies are often needed to discern those patterns.

Although local, county, state, and territorial health departments bear the chief responsibility for monitoring the incidence of infectious diseases and antibiotic resistance, budget cutbacks over the past decade have reduced those surveillance efforts substantially (13, 21). Most federal resources are now channeled into meeting concerns raised by the HIV epidemic as well as the recent upsurge of multidrug-resistant mycobacteria. In addition, there are continuing needs to monitor the incidence of sexually transmitted diseases (STDs) and vaccine-preventable diseases. The surveillance efforts for the above four categories of diseases account for about 85% of the total annual CDC budget. These budgetary mandates leave very little in the way of resources for monitoring other infectious diseases or for tracking the emergence of antibiotic resistance.

State and local resources that might help to extend surveillance to diseases that lie outside the federally specified areas of AIDS, tuberculosis, and STDs have been reduced and increases are not likely to be forthcoming, particularly because states are prohibited from deficit budgeting. At the state and territorial levels, these reductions in surveillance budgets have led to personnel shortages and mean that there are typically no full-time personnel or perhaps even part-time individuals doing routine surveillance of these additional infectious diseases, including food- and water-borne illnesses, that fall outside federal mandates. In 1992, less than $55,000 was spent at the federal, state, and local levels for monitoring of antibiotic resistance through the national notifiable disease reporting system (13). The amount has not increased substantially over the past two years.

Several other somewhat limited and underfunded forms of infectious disease surveillance are in place. They include the National Nosocomial Infection Surveillance System (NNIS), which is a voluntary program for tracking the incidence of infections in standard and intensive care units at selected hospitals as well as a nosocomial network within the Veterans Administration Hospital. However, the NNIS program is not representative of all geographic areas or hospital types, and it does not provide information on antibiotic-resistant bacteria in the community.

Because antibiotic resistance patterns may vary locally and regionally, surveillance data need to be gathered locally, at least from selected sentinel sources. Patterns can change very rapidly, and they need to be monitored closely because of their important implications for how individual physicians practice medicine as well as for public health in general. Thus, recognition of these changing patterns of antibiotic resistance can affect how physicians treat patients, which for many routine (or seemingly routine) infections is done empirically.

Most hospitals in the public sector are facing budgeting cutbacks that threaten their quality of work, decrease their ability to screen for resistance, and decrease their incentive to send resistant strains to local and state public health laboratories as well as to the CDC. Health care networks in the private sector, including large-scale health maintenance organizations, and many private practices tend to use large commercial laboratories whose main goal is profit. Thus far, these laboratories have done little to summarize and report antibiotic resistance data, and it is generally felt that such data, even if they were available, are not suited for the purpose of monitoring the emergence of antibiotic resistance.

Other impending economic factors could make these problems worse. For example, as regional and global trade barriers are lowered, imported meats, fruits, vegetables, and other foods could become an important source of antibiotic-resistant infectious diseases—particularly from developing countries. In developing countries, antibiotic resistance is even higher due to over-the-counter sale of antibiotics and almost total lack of antibiotic resistance screening. Several recent outbreaks of food-borne illness in Minnesota involving imported fruits and vegetables lend support to this assertion that increased rather than reduced surveillance is urgently needed.

In addition, surveillance of disease and antibiotic resistance in animals is under the auspices of the Animal and Plant Health Inspection Service within the U.S. Department of Agriculture. Current activities of the American Association of Veterinary Laboratory Diagnosticians and National Committee for Clinical Laboratory Standards (NCCLS) include a program to develop standardized procedures for antibiotic sensitivity testing in agriculturally relevant pathogens following guidelines comparable for those used for human pathogens. However, this is a very limited program.

In summary, there are no national surveillance programs for either human or veterinary pathogens, and thus, available data on the incidence of antibiotic resistance in this country probably represent only the tip of the iceberg.
RECOMMENDATIONS

There is an urgent need for effective domestic and global surveillance of antibiotic resistance in animals and humans. There is also an urgent need for more prudent use of antibiotics in both human and veterinary medicine, particularly as it relates to food production. Of equal urgency is the need for better hospital infection control and implementation of guidelines to reduce spread of infection and antibiotic-resistant pathogens in the hospital environment. There is a great need for strengthening the curriculum of human and veterinary health care professionals in the areas of sterilization and disinfection, mechanisms of antibiotic resistance, and factors contributing to its spread, including inappropriate antibiotic usage. There is also a need for patient education regarding appropriate uses of antibiotics. More basic research is needed to more clearly delineate mechanisms of antibiotic resistance and to identify new antimicrobial targets. Lastly, greater emphasis must be placed upon research related to rapid, reliable diagnostic tests and vaccines for prevention and control of infectious diseases.

I. National Antimicrobial Surveillance System

A. Indications

The most compelling indication for a national surveillance system is that no such system currently exists. Recent advances now make it possible for clinical and reference laboratories to accurately assess the susceptibility of a wide variety of bacterial and fungal pathogens via standardized methods. Medical informatics and computer technology are now available for accurate collection, efficient transmission, and timely analysis of surveillance data which will allow the information to be disseminated in a site-specific manner. Implementation of a surveillance system with necessary quality assurances and fiscal support will allow the generation of antimicrobial resistance data needed for decision-making regarding therapy and/or prophylaxis. Data will be forthcoming to predict emerging resistances among available therapeutic drugs, leading to effective interventions that could control dissemination of resistance.

B. Considerations

1. National surveillance system should do the following

   a. Focus on the most prevalent bacterial and fungal pathogens (not viral) that concern human health. This will assess isolates from clinical disease cases and routine isolates so that no bias from one center testing only the “problem” isolate or more resistant isolates compromises the results. Attention will be given to the trend in upward “creep” of MICs. There is also a need to monitor food sources such as animal products at the supermarket level as well as imported fruits, vegetables, and other products that may carry colonizing, drug-resistant bacteria and colonizing fecal flora in some patient populations. Salmonella and Shigella both should be monitored. Salmonella gives the best window into the impact of uses of antibiotics in the animal world, and the fraction of Shigella that is imported gives us an excellent view of the impact of antibiotic uses in the developing world (20). Monitoring of soil waste in farms should also be considered.

   b. Establish a baseline of antimicrobial in vitro efficacy to which the following can be compared: earlier data from similar surveillance studies found in medical literature reviews, especially if these studies utilized comparable methodologies and surveillance techniques; subsequent surveillance data resulting from the establishment of a national surveillance system analyzed in a longitudinal manner; non-U.S. data to assess the international risks of resistance.

   c. Accumulate concurrent demographic profile information to assess the relationships between organisms emerging in hospitals of various sizes or disease therapy focuses and pathogens prevalent among ambulatory patients in the community and animals housed in various environments. The role of drug use in these environments shall be addressed.
d. Establish a mechanism whereby organisms possessing certain **phenotypic** and **genotypic** resistance patterns will be referred to adequately funded laboratories for detailed study. Various molecular typing and investigative procedures can lead to earlier understanding of developing resistance mechanisms and spread of epidemic clones.

e. Allow for the future assessment of the encountered resistant pathogens’ effect on patient outcomes, general community health, and the costs of health care delivery. Surveillance will target areas for specific intensive interventions for prevention (like vaccine campaigns and antimicrobial use reduction programs). Surveillance will also identify areas where epidemiologic investigations are needed to improve understanding of spread of drug-resistant strains and to identify ways to interfere with spread.

f. Maximize the possibility that data will lead to significant forms of professional health care intervention to reduce the probability that resistance to the drug will be spread widely and have an adverse impact on the national quality of health care outcomes. Interventions ideally should be focused at the local level but regional and national interventions could also provide great benefits.

g. Provide expert federal agencies and societies the information to modify recommendations regarding therapy or prophylaxis of diseases or regarding testing procedures. These can be implemented at various levels related to patient or institutional demographics or by geography (local, regional, national).

h. Provide a compatible system in which subsets of participants could be grouped for common benefits. Examples include federal hospitals (Veterans Administration [VA], military, etc.), animal care facilities (university-based, U.S. Department of Agriculture [USDA], etc.), recognized HMO-like programs, and academic institutions such as university teaching hospitals.

i. Provide the accumulated data to pharmaceutical manufacturers, thus providing the validations of contemporary drug spectrums. This will be valuable in establishing meaningful organism coverage indications in antimicrobial agent package inserts.

j. Provide a system that can be modified to address any discovered area of concern related to the effective therapy of infectious organisms. This could allow expansion to cover fungi, viruses, cell-associated organisms, and some parasites.

2. Monitoring of organisms

a. Bacterial pathogens considered important in human and animal infections should be monitored. Suggestions are included in Appendix B. The choices should be selected and updated periodically based on the frequency with which these agents cause disease, the human or animal morbidity and economic impact of resistance in that species if it occurs or increases, the perceived threat of genomic mutation, and the need to confirm the continued efficacy of important therapeutic antimicrobial agents.

b. Some strains/species shall be tested on a regular schedule (quarterly) and others as dictated by the needs of the surveillance oversight **panel** or requirements for spectrum validations as part of the interaction with industry colleagues (spectrum data for drug package inserts).

c. The numbers of organisms tested should be significant (final counts depending on number/species/site and the numbers of participant sites) and should be finalized with input from medical statisticians.

d. Some isolates will require the choice of participants that routinely test unusual species (referral centers) or, in the case of some animal pathogens, those geographic specialty laboratories having expertise with a single pathogen or a group of pathogens specific for a single animal species, e.g., swine, cattle, or sheep.

e. Some species may be added that represent unusual organisms from which documented resistance genomes have been transferred to prevalent human pathogens (examples: viridans group streptococci and oral **Neisseraspp.**).
3. Geographic locations of participants

a. A representative sample of organisms can be achieved only by a broad sampling of geographically dispersed laboratory isolates. Preliminary ideas for selection include the following.

i. Laboratories should be chosen according to U.S. population density by state. Local and state public health laboratories should be involved in data collection but should not be the sole participants.

ii. States should be grouped into regions that should not be significantly different than those used in the CDC Morbidity and Mortality Weekly Report.

iii. Participants should represent demographic populations of patients and organisms within their states or regions. Examples would include laboratories from large and small (≤250 beds) hospitals plus samples from microbiology laboratories servicing outpatient clinic practices. Distribution of centers based on hospital bed size should be encouraged.

b. The above ideas will focus on human pathogen surveillance. Smaller numbers of participants will contribute the animal pathogens which will also be geographically diverse and hopefully representative for the animal species/pathogen population data.

c. In general there is a need for one monitoring site per 1,000,000 to 2,000,000 people, supplemented by animal pathogen participants and important demographic subsets (VA medical centers, etc.). Distribution of centers based upon hospital bed size should be encouraged, with regional centers being considered in areas where patients are more widely dispersed. Not all locations will have to be recruited in the first year, but representative participants from each region should be sought as early as possible.

4. Monitoring of populations

a. Demographic profiles of the hospital/laboratory will be required for participation (updated each year). This would allow initial classification of participants by various parameters such as hospital size, services offered, formulary practices, antimicrobial use patterns, infection control practices, teaching status, etc.

b. Particularly important surveillance groups will be selected by:

i. Hospital size.

ii. Services or teaching offered.

iii. Health care delivery classification (HMO, federal, VA, private, etc.).

iv. Clinic practice.

v. Hospital-acquired pathogens versus pathogens from other sources.

vi. Prior antimicrobial therapy and type.

vii. Others.

c. Given the limited testing done by commercial laboratories, a systematic approach for measuring community-acquired antibiotic-resistant bacteria must be established. This task might best be performed by the local and state health departments.

5. Methods

a. All methods used should be of reference quality and should closely follow the documents published by the NCCLS.
b. Where possible, initial screening should use the disk diffusion method (NCCLS M2-A5) for those pathogen-antimicrobial combinations that can be accurately tested.

c. A subset of organism/antimicrobial combinations will require special tests that will need referral to a reference laboratory or laboratories. Alternatively, these generally fastidious species can be tested at each location by some newer technologies, if costs and reagent availability dictate.

d. Method choices should be focused through an advisory panel of experts in the field of antimicrobial susceptibility testing.

e. Rigid quality controls (QC) will be necessary for each participant (local) laboratory, each monitoring reference laboratory, and any laboratory used for special contracted tests or molecular studies. Only data obtained by accepted methods and accompanied by validating QC should be entered into the antimicrobial surveillance database. Participants regularly not complying with QC guidelines should be replaced.

6. Locations of pathogen testing

a. The dominant, quarterly testing should be performed at the laboratory participant locations.

b. Specific pathogens (identified by species, resistance phenotype, isolate origin, etc.) should be routinely forwarded to secondary, reference (monitor) laboratories. These centers should perform contracted studies by specified methods (protocol) and report results to the U.S. antimicrobial surveillance data processing location (i.e., CDC [see below]).

c. Molecular typing, resistance mechanism studies, and other molecular-level techniques will be necessary on an annual basis. These studies should be assigned to appropriate reference laboratories as required by the surveillance administrators.

7. Format for data

a. All data should be expressed as quantitative endpoints regardless of method. This dictates measurement of disk diffusion tests by calipers to the nearest whole millimeter and the use of MIC endpoints in micrograms per milliliter for dilution methods. Such measurements will facilitate the recognition of susceptibility changes within categories (qualitative) established by the NCCLS.

b. Qualitative interpretations shall be applied objectively by computer programs based on current NCCLS tables. Similarly, QC guidelines found in the NCCLS tables should also establish the validity of each participant’s/referee’s data.

8. Data entry and analyses

a. Surveillance studies of all types can greatly benefit from well-structured computer systems. Prior studies performed by the CDC (NNIS and Public Health Laboratory Information System), WHO (WHONET), and private parties have effectively utilized relatively simple data input programs. Such software is available and/or programmable without the significant risk of problems. Timeliness, flexibility, and the ease of expanding the pyramidal reporting structure are important considerations.

b. All input should be simplified to include minimal transcriptions via digital reading, bar-coding, disk transfers, or modem networking.

c. A single data analysis location would be preferred. Programming would be under the direction of the surveillance oversight panel, which should also periodically review the analysis results.

d. Simple in-laboratory work forms should also be standardized for all locations as a hard-copy backup. These forms should not greatly differ from the clinically used forms at each location.
e. Previously organized, computerized networks can be used as models. Possible collaborations might include CDC-NNIS, CDC-STD regional surveillance in Neisseria gonorrhoeae, VA networks, SCOPE (University of Iowa program), and international programs through various medical specialty societies.

9. Frequency of analysis and access

a. Preliminary guidelines for the surveillance are as follows.

i. Surveillance of basic pathogen group by each participant at the local site—QUARTERLY.

ii. Analysis of special (usually fastidious) pathogens by a selected number of reference or special skill laboratories—QUARTERLY.

iii. Expanded list of antimicrobial agents and pathogens that will satisfy annual validation of drug package insert spectrum—YEARLY (winter quarter).

iv. Special studies as directed by the oversight panel—VARIABLE.

b. The program must establish the perception that participation is a benefit. To accomplish this goal the following items might be considered.

i. Quarterly reports to all participants.

ii. Annual newsletter summary of results.

iii. Publications generated from surveillance data acknowledging the participation of all sites.

iv. Participant interaction with the database. Confidentiality should be maintained by coding locations and limiting laboratory-defined access to the participant center only. However, data would otherwise be available but audited by the oversight panel or study administrators.

v. Periodic meeting of the surveillance participants, at a national meeting or as a free-standing annual symposium.

10. Organization of the surveillance system

a. Funding should be sought from all parties that would derive a significant benefit from the system. These include, but would not be limited to (a consortium approach), the following.

i. Federal and state agencies: CDC, Food and Drug Administration (FDA) (several components), National Institutes of Health (NIH), USDA, state health departments, VA, and Department of Defense.

ii. Industry: Pharmaceutical manufacturers, reagent manufacturers (antimicrobial tests and microbiology media), drug delivery systems, health care delivery and hospital corporations, and contract research organizations.

iii. Academic institutions, professional societies and university medical centers

b. An oversight panel should be established for the surveillance study network. This panel should include representatives from the principal federal agencies, members of the scientific community at large who are experts in antimicrobial resistance, specialists in infectious disease and in vitro antimicrobial testing in animals and humans, experienced personnel in multilaboratory surveillance, hospital/health care epidemiologists, computer and statistical analysts conversant with antimicrobial issues, and representatives of industry as dictated by consortium participation. The Antimicrobial Resistance Surveillance Program should be located within the National Center for Infectious Diseases at the CDC. This would allow integration with other surveillance activities for infectious diseases by experts in microbiology.
and epidemiology. Because of the CDC's track record and proven expertise, this is the logical location for a national surveillance system.

c. If this program is successful in meeting the cited goals and objectives, cost savings to the national health care system could easily be in the hundreds of millions of dollars. A few areas of greatest impact are (i) the focusing of pharmaceutical research as early as possible on emerging drug resistance problems; (ii) the reduction of drug development costs by placing new compounds into the system to establish in vitro spectrums (cost rates would be less than the multiple individual grants to independent investigators); (iii) validation of current compound spectrums annually, reducing manufacturers' costs for independent vendor contracts (like item ii); (iv) availability of contemporary, localized data to federal and state agencies, enabling them to identify emerging resistances or pathogen frequencies and thus develop early interventions and selections of affective therapeutic regimens or prophylactic modalities; and (v) other interventions stimulated by the data derived from the surveillance, leading to greater cooperation among government, industry, and professional components of the health care system at large.

11. Immediate recommendations

a. Convene an expert panel to develop surveillance protocol and establish an annual budget. The above outline could be used as a preliminary or tentative plan. Federal funding should be immediately identified for the national surveillance system, and several agencies (CDC, FDA, NIH, VA, USDA, etc.) as well as other sources should be involved in funding decisions.

b. Seek appropriate expertise in statistical analysis for determination of organism sample sizes, population-based participant selection, and computer support for analyses.

c. Initiate an extensive search for earlier surveillance databases on resistance generated from U.S. multicenter investigations performed with NCCLS or compatible methods. Also expand that literature search to worldwide surveillance data, if available.

II. Recommendations Related to Emergence of Resistance

Many unanswered questions surround the role of animals and the microbiota in antibiotic resistance. The use of subtherapeutic levels of antibiotics for prophylaxis and as growth promoters continues to be a concern. Current aquaculture practices also raise concerns. Systematic studies are needed to determine how much of our clinical problem of antibiotic resistance can be traced to these phenomena.

At the health care level, community- and hospital-based practices should be studied from a behavioral standpoint to determine what practices may contribute to emergence and spread of antibiotic resistance and how they might be modified.

Professional and public education should be strengthened in the area of infectious diseases and antibiotics so as to reduce inappropriate usage of antibiotics. The curriculum of health professional (medical, dental, nursing, and veterinary) school and postgraduate educational programs should be strengthened in the areas of sterilization, disinfection, and antibiotic resistance. This should result in reduction of spread of infectious agents and more prudent use of antibiotics.

Educational materials should be developed and widely distributed to patients and to food producers. The need for partnerships in improving antimicrobial use for cost-effective treatment of infections and to preserve the effectiveness of antimicrobial drugs for the future should be emphasized.

Key federal agencies, including the NIH, CDC, and USDA, should develop more information on the impact of infectious diseases and better means for conveying information to representatives from pharmaceutical and biotechnology companies, health care organizations, elected officials, and the general public.

To preserve the extraordinary gains made by antimicrobial agents against the battle of infectious diseases will require more imaginative, collective action by governments, the pharmaceutical industry, health care providers, and consumers. No one group or country can accomplish this goal alone. Resistant microorganisms do not recognize geographic boundaries. Inappropriate or excessive use of antimicrobial drugs by any
person or practitioner can affect the entire ecologic system and cannot be condoned. Attention must be focused on societal issues that determine how these drugs are used and on the establishment of policies that will result in more selective and rational use of antimicrobial drugs.

III. Research and Drug Development Needs

There is an urgent need for more basic research directed toward development of new antimicrobial compounds but also toward development of effective vaccines and other prevention measures. In FY 1994 allocations to the National Institute of Allergy and Infectious Diseases of the NIH for funding of non-AIDS infectious disease research were reduced by $20 million (21). Increased appropriations are urgently needed to fund areas of research directly related to new and reemerging infections and antibiotic resistance.

More basic research is needed to delineate the genetic and metabolic pathways, including essential regulatory factors, that determine virulence as well as antibiotic susceptibility or resistance in pathogens of human and veterinary importance. To conduct this research, better, more consistent measures of antibiotic resistance are needed, and a culture collection containing representative antibiotic-resistant biotypes and genotypes should be developed. More resources should be devoted to the sequencing of the entire genome of microbial pathogens in an attempt to identify common antimicrobial targets. Such studies are expected to help in identifying novel targets for molecules that interfere specifically with essential physiological steps of pathogens. Traditional empirically based screening of potential inhibitors of pathogens is believed to be too crude to unveil such targets.

Screening procedures have been modernized so that tens of thousands of compounds can be tested on a daily basis. Eventually, such strategies for drug development taken together with better, quicker, and more precise diagnostic technologies could lead to a new, more highly focused approach for dealing with infectious diseases that could be associated with economically attractive niche markets.

Nonetheless, conservative marketing projections have led many companies to reduce—or, in some cases, disband—their antibiotic drug discovery and development programs in this country but not in other countries like Japan. Because such projections are misleading, if not outright wrong, company marketing specialists should participate in discussions of the problem of emergent antibiotic resistance and they should be involved in efforts to identify incentives for basic and applied research in this area that would contribute to the development of new antibiotics or other novel entities to inhibit pathogens. It is also recommended that representatives from national and regional HMOS be consulted on such matters because of the increasing cost of treating antibiotic-resistant infections and the escalating use of the most expensive, recently introduced agents for prophylaxis or empiric therapy.

Other efforts to encourage antibiotic drug research and development that involve federal agencies, universities, and companies in the private sector should be encouraged. Other factors which may be considered to encourage discovery of new agents may be tax benefits for companies engaged in such research and development and the issue of litigation problems. Existing efforts in other health-related areas, such as the National Cooperative Drug Discovery Development Groups for the development of anticancer drugs and the National Vaccine Program, should be reviewed. Potential models for a new program to coordinate research on new drug development should be explored, including extending the useful patent life of drugs. An orphan-drug-like concept for novel narrow-spectrum drugs for treating specific pathogens and perhaps the use of a treatment-IND approach to allow licensing and sale of new anti-infective products at an earlier stage of development than is now permitted should be considered.

The need for partnerships in order to make drugs more readily available, to improve usage, and to develop new products cannot be overemphasized. For example, it should be to the advantage of the pharmaceutical industry to support national policies that require better quality control, proof of safety and efficacy, and assurance of patent protection (22). Likewise, it should be realized that the research-intensive pharmaceutical industry is the source for most new drugs and that industries need to profit from their investments in order to pay for the research.

In return for help from the government in providing a more stable market for their products, industry should help support national efforts (scientific organizations, foundations, and educational institutions) whose role it is to educate people about the appropriate use of antibiotics, to improve the availability and distribution of effective drugs, to monitor the emergence of resistant strains, and to train young investigators in therapeutics (22).
The laws of evolution dictate that microbes will eventually develop resistance to practically any antibiotic. Thus, more basic research is needed to facilitate development of effective vaccines. For other infectious diseases, better nonvaccine prevention measures are needed to target environmental or behavioral factors that contribute to pathogen transmission. Support for more research is needed to facilitate development of better infection control technologies in several arenas, for example, water treatment, food production, hospital hygiene, and vector control.

REFERENCES

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# Appendix B

## Suggested Organisms To Be Included in Antibiotic Resistance Surveillance Program

<table>
<thead>
<tr>
<th>Organism(s)</th>
<th>Antimicrobial agent(s)</th>
<th>Method preferred (screening)</th>
<th>Frequency/scope</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococci</em> (Enterococcus faecalis, E. faecium)</td>
<td>Vancomycin, Ampicillin, Gentamicin—HLR, Streptomycin—HLR, (Teicoplanin), (Chloramphenicol), (Doxycycline), (Fluoroquinolone), (β-Lactamase test)</td>
<td>Disk</td>
<td>4/All</td>
</tr>
<tr>
<td><em>Streptococci</em> (Pneumococcus, <em>serogroups A and B, and viridans group</em>)</td>
<td>Penicillin, Macrolide, Trim/Sulfa, Cephalosporin [3rd], Vancomycin, Chloramphenicol, (Cephalosporin [2nd])</td>
<td>Dilution</td>
<td>4/All (referred)</td>
</tr>
<tr>
<td>Staphylococci (Staphylococcus aureus, <em>CNS</em>)</td>
<td>Oxacillin, Macrolide, Vancomycin, (Fluoroquinolone), (Rifampin)</td>
<td>Disk</td>
<td>4/All</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Penicillin, Tetracycline, Cephalosporin [3rd], Fluoroquinolone, Trim/Sulfa, (β-Lactamase test)</td>
<td>Dilution</td>
<td>CDC-STD monitoring system</td>
</tr>
<tr>
<td>Xanthomonas maltophilia</td>
<td>Trim/Sulfa, BLIC, Fluoroquinolone, Tetracycline, Cephalosporin [3rd]</td>
<td>Dilution</td>
<td>1/All (referred)</td>
</tr>
<tr>
<td>Campylobacter spp., Helicobacter pylori, <em>Vibrio</em> spp.</td>
<td>Peridng species-dependent selection</td>
<td>Dilution</td>
<td>1/Focused (referred)</td>
</tr>
</tbody>
</table>

Note: HLR = Hinton-Lawrence test, LDR = Low-Dosage Rapid Test, BLIC = Biological Indicator Test for Colonisation, CNS = Central Nervous System.
<table>
<thead>
<tr>
<th>Organism(s)**</th>
<th>Antimicrobial agent(s)*</th>
<th>Method preferred (screening)</th>
<th>Frequency/scope ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em> group</td>
<td>Metronidazole, Carbapenem, BLIC, Clindamycin, Cephamycin, Cephalosporin [3rd] (Chloramphenicol) (β-Lactamase test)</td>
<td>Dilution</td>
<td>4/Focused (referred)</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Metronidazole (Vancomycin (Teicoplanin))</td>
<td>Dilution</td>
<td>I/Focused (referred)</td>
</tr>
<tr>
<td>Bacterial vaginosis-associated pathogens (Peptostreptococcus spp., Gardnerella vaginalis, Mobiluncus spp., Prevotella spp.)</td>
<td>Metronidazole, Clindamycin, Ampicillin, Trim/Sulfa, Cephalosporin [3rd] (Cephamycin) (Cephalosporin [3rd]) (Carbapenem) (BLIC)</td>
<td>Dilution</td>
<td>I/Focused (referred)</td>
</tr>
<tr>
<td>Veterinary pathogens (Haemophilus somnus,* Actinobacillus pleuropneumoniae,* Bordetella bronchiseptica, Pasteurella spp., etc.)</td>
<td>(list dictated by Federal regulation if food animals or by vet prescription availability)</td>
<td>Dilution</td>
<td>I/Focused (referred)</td>
</tr>
<tr>
<td><em>Mycobacteria</em>³</td>
<td>(Pending species selection)</td>
<td>Dilution and species dependent</td>
<td>4/Focused (referred)</td>
</tr>
<tr>
<td><strong>N. meningitidis</strong>*</td>
<td>Penicillin, Cephalosporin [3rd] Fluoroquinolone, Rifampin, Trim/Sulfa (β-Lactamase test)</td>
<td>Dilution (E)</td>
<td>4/All (referred)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em>³ (may be grouped by serogroup B and others)</td>
<td>β-Lactamase test, Ampicillin, Chloramphenicol, Trim/Sulfa, Cephalosporin [3rd] Macrolide, Fluoroquinolone BLIC (Cephalosporin [1st, 2nd, oral])</td>
<td>Disk or dilution</td>
<td>4/AH</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Aminoglycoside, Penicillins [3rd] Trim/Sulfa, Fluoroquinolone, Carbapenem</td>
<td>Disk</td>
<td>4/All</td>
</tr>
<tr>
<td><em>Aeromonas hydrophila</em></td>
<td>Ampicillin, Aminoglycoside, Cephalosporin [3rd] Fluoroquinolone Trim/Sulfa (Penicillin [3rd]) (Carbapenem)</td>
<td>Disk</td>
<td>I/All</td>
</tr>
<tr>
<td>Organism(s)&quot;</td>
<td>Antimicrobial agent(s)</td>
<td>Method preferred (screening)</td>
<td>Frequency/scope&quot;</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------</td>
<td>-----------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>Ampicillin Macrolide Cephalosporin [1st, 2nd, 3rd] Tetracycline Trim/Sulfa BLIC Fluoroquinolone</td>
<td>Disk</td>
<td>4/All</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>Ampicillin Aminoglycoside Cephalosporin [3rd] BLIC Fluoroquinolone Carbapenem Trim/Sulfa</td>
<td>Disk</td>
<td>4/All</td>
</tr>
</tbody>
</table>

"Primary" indicates the need for routine susceptibility surveillance because of the high medical care impact of antimicrobial resistance. "Secondary" indicates a reduced impact or a minimal current frequency of the pathogen (real or low isolation rates) in human or animal disease. *, highest priority. CNS, coagulase-negative staphylococci.

Some agents are listed by class because a marker compound could be selected to represent a group of drugs sharing high levels of cross-resistance (examples: fluoroquinolones, generations of cephalosporins [given in brackets], aminoglycosides, etc.). BLIC, β-lactamase inhibitor combinations. Penicillin [3rd], either mezlocillin or piperacillin, HLR, high-level resistance. Trim/Sulfa, trimethoprim-sulfamethoxazole. Drugs in parentheses are those which could be added to screen for resistance phenotypes or to provide data on alternative therapeutic regimens.

"Frequency" specifies the number of times that a pathogen is audited per year: 4, quarterly; 1, once annually. "Scope" indicates the participants involved in sampling the isolates: All, all participant laboratories; Focused, a selected subset of laboratories.

Screened mycobacteria would include *M. tuberculosis*, *M. avium*-intracellulare complex, *M. koi*, and rapid growers (*M. chelonae*, *M. fortuitum*).